HUMAN MONOCLONAL ANTIBODIES THAT NEUTRALIZE PANDEMIC GII.4 NOROVIRUSES

PRIORITY CLAIM

[0001] This application claims benefit of priority to U.S. Provisional Application Ser. No. 62/723,155, filed Aug. 27, 2018, and U.S. Provisional Application Ser. No. 62/723,565, filed Aug. 28, 2018, the entire contents of both applications being hereby incorporated by reference.

[0002] This invention was made with government support under NIH Grants P30DK058404, P01AI057788, P30CA125123 and T32GM120011 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

1. Field of the Disclosure

[0003] The present disclosure relates generally to the fields of medicine, infectious disease, and immunology. More particular, the disclosure relates to human antibodies binding to human norovirus.

2. Background

[0004] Since the licensure and use of rotavirus vaccines, human noroviruses (HuNoV) have become the major etiologic agent of epidemic and sporadic acute gastroenteritis (Glass et al., 2009). The persistence of HuNoVs is attributed to many factors, such as a low infectious dose, extreme environmental viral stability, high levels of shedding, and prolonged shedding even after symptoms have resolved (Fields et al., 2013). According to the Centers for Disease Control and Prevention, HuNoVs cause on average 19 to 21 million cases of infection and between 570 to 800 deaths in children under the age of five each year in the United States. HuNoVs infect people of all ages and, even though infection is characteristically acute and self-limiting, disease can become life threatening in children, the elderly, and the immunocompromised (Bok and Green, 2012). The correlates of HuNoV immunity in humans are poorly incompletely understood. There are several correlates of protection that have been described; the new capacity to perform in vitro neutralization testing described here may provide an improved correlate. Antibodies are clearly important to human immunity (Atmar et al., 2018).

[0005] One of the challenges for developing antibodies or vaccines to prevent HuNoV-associated disease is the extreme antigenic diversity of field strains. HuNoVs currently are classified phylogenetically into 7 different genogroups (GI-GVII) and at least 41 different genotypes (Vinjé, 2015). Viruses from genogroup I (GI) and the rapidly evolving genogroup II (GII) account for nearly all human infections. The HuNoV genome contains 3 open reading frames (ORF1, ORF2, and ORF3). ORF1 encodes nonstructural proteins, while ORF2 and ORF3 encode the major and minor capsid proteins, respectively. In the past, HuNoVs could not be cultivated in cell culture, but the VP1 and VP2 protein sequences could be expressed using a baculovirus expression system to produce HuNoV virus-like particles (VLPs) (Jiang et al., 1992). These VLP reagents have facilitated the study of HuNoV evolution, antigenicity and the emergence of new virus strains (Richardson et al., 2013; Erdman et al., 1989).

[0006] Since the mid-1990s, viruses from genogroup II genotype 4 (GII.4) have caused the majority of outbreaks, with new strains emerging every 2-3 years (Vinjé, 2015). In 2012, the GII.4 Sydney strain emerged and since then has continued to predominate among circulating strains. The molecular basis for antibody-mediated recognition of these strains and their mechanisms of action are not well characterized.

SUMMARY

[0007] Thus, in accordance with the present disclosure, there is provided a method of detecting a norovirus infection in a subject comprising (a) contacting a sample from the subject with an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively; and (b) detecting norovirus in the sample by binding of the antibody or antibody fragment to a norovirus antigen in the sample. The sample may be a body fluid, such as blood, sputum, tears, saliva, mucous or serum, semen, cervical or vaginal secretions, amniotic fluid, placental tissues, urine, exudate, transudate, tissue scrapings or feces. Detection may comprise ELISA, RIA, lateral flow assay or Western blot. The method may further comprise performing steps (a) and (b) a second time and determining a change in norovirus antigen levels as compared to the first assay.

[0008] The antibody or antibody fragment may be encoded by clone-paired variable sequences as set forth in Table 1, may be encoded light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1, or may be encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1. Alternatively, the antibody or antibody fragment may comprise light and heavy chain variable sequences according to clone-paired sequences from Table 2, may comprise light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2, or may comprise light and heavy chain variable sequences having 95% identity to clone-paired sequences from Table 2. The antibody fragment may be a recombinant scFv (single chain fragment variable) antibody, Fab fragment, F(ab')2 fragment, or Fv fragment.

[0009] In another embodiment, there is provided a method of treating a subject infected with norovirus or reducing the likelihood of infection of a subject at risk of contracting norovirus, comprising delivering to the subject an antibody or antibody fragment having clone-paired heavy and light chain CDR sequences from Tables 3 and 4, respectively. The antibody or antibody fragment may be encoded by clone-paired variable sequences as set forth in Table 1, may be encoded light and heavy chain variable sequences having 70%, 80%, or 90% identity to clone-paired variable sequences as set forth in Table 1, or may be encoded by light and heavy chain variable sequences having 95% identity to clone-paired sequences as set forth in Table 1. Alternatively, the antibody or antibody fragment may comprise light and heavy chain variable sequences according to clone-paired sequences from Table 2, may comprise light and heavy chain variable sequences having 70%, 80% or 90% identity to clone-paired sequences from Table 2, or may comprise light